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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,396	04/14/2006	Jean-Charles Schwartz	P08824US00/BAS	8440

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EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
04/12/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,396	SCHWARTZ ET AL.	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-62* is/are pending in the application.

4a) Of the above claim(s) *34 and 39-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-33 and 35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 (national stage application) of PCT/FR04/01628, filed on 6/25/2004.

Priority

This application, filed on 4/14/2006, is a national stage application of PCT/FR04/01628, file don 6/25/2004, and claims foreign priority to Application No. 0307836, filed on 6/27/2003. Copies of the PCT and foreign applications have been received. However, the foreign application is not in English, was not accompanied by an English translation, or an English language abstract. An English language translation or abstract is respectfully requested for the foreign application. Therefore, the priority date and effective filing date given to the instant claims is 6/25/2004.

Response to Remarks

1. Applicant's arguments, regarding the rejection of claims 30-33 and 38 under 35 USC § 112, first paragraph, have been fully considered and are found persuasive. The claims have been amended to remove 'polymorphic crystalline structures' of the claimed compounds. In view of the claim amendments, this rejection is withdrawn.

Applicant's arguments, regarding the rejection of claims 27-33 for obviousness type double patenting over claims 25-28 of co-pending Application No. 11/815376 have been fully considered, but are not found persuasive. The claims have been amended to exclude chlorohydrate salts of 3-(4-chlorophenyl)propyl-3-piperidinopropylether, to which the co-pending claims are drawn. The Applicants have stated that due to the

claim amendments, the rejection for obviousness type double patenting should be withdrawn. The examiner disagrees. Pharmaceutically acceptable salts of compounds are well known in the art; therefore, it would have been prima facie obvious to prepare various salts, such as the chlorohydrate salt, of the compounds in the claimed composition. The rejection is maintained, for reasons of record. For Applicant's convenience, this rejection will be reiterated in the office action.

Applicant's remarks, regarding the rejection of claims 27-33 and 35-38 under 35 USC § 103(a) have been fully considered, but are not found persuasive. The Applicants state that the claims would not have been prima facie obvious at the time of the invention over Todd, in view of Schwartz, because Todd does not teach the combination of olanzapine with histamine H_3 receptor antagonists, and Schwartz does not teach that H_3 receptor antagonists can be administered with psychiatric agents to reduce weight gain. The examiner respectfully disagrees. Todd teaches that administration of antipsychotic agents such as olanzapine are associated with side effects such as weight gain, and that to reduce such side effects, olanzapine is administered with H_2 receptor antagonists. Schwartz et. al. teaches that histamine H_3 receptor antagonists such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether can be administered along with psychiatric agents to improve their efficacy and reduce the associated side effects. Additionally, Schwartz et. al. teaches that histamine H_3 receptor antagonists are used to treat cognitive deficits, attention deficits, and obesity. It would have been expected that in treating obesity, weight gain would have been reduced. Therefore, as the prior art teaches that both histamine H_2 and H_3 receptor antagonists can be combined with

antipsychotics such as olanzapine to reduce side effects, and that both types of histamine receptor antagonists reduce weight gain, one of ordinary skill in the art would have been motivated to combine a histamine H_3 receptor antagonist, such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, with olanzapine, for the purpose of increasing the efficacy of olanzapine while reducing side effects, such as weight gain.

The Applicants have argued that the replacement of histamine H_3 receptor antagonists for H_2 receptor antagonists in the composition taught by Todd would not have been obvious, due to the differences in biological activity between these antagonists. While this argument has been fully considered, it is not found persuasive. Todd teaches that histamine H_2 receptor antagonists reduce side effects such as weight gain associated with use of olanzapine, while Schwartz et. al. teaches that histamine H_3 receptor antagonists can be administered with psychiatric drugs to reduce side effects. Particularly, Schwartz et. al. teaches that histamine H_3 receptor antagonists are used to treat obesity. By treating obesity, weight gain would have been reduced as a result. Therefore, as both histamine H_2 and H_3 receptor antagonists are taught to be administered with psychiatric agents, and to be used to reduce weight gain, it would have been obvious to administer a histamine H_3 receptor antagonist such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether with olanzapine, for the purpose of reducing side effects such as weight gain. The rejection was proper and is maintained, for reasons of record. For Applicants' convenience, this rejection will be restated in the office action. Accordingly, this action is made FINAL. Claims 41-62 were withdrawn previously due to the restriction and species requirement. As in the previous office

action, the claims have been examined with regards to the elected species of (a) olanzapine as the antipsychotic; and (b) 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether as the histamine H_3 receptor antagonist.

2. Claims 27-33 and 35-38 were examined.

3. Claims 27-33 and 35-38 are rejected.

Claim Rejections-35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

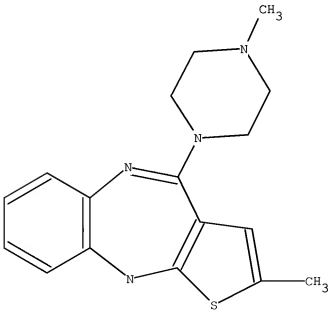
3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 27-33, and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Todd, WO 00/74784 patent application publication, in view of Schwartz et. al., US 7,138,416 patent.

5. Instant claims 27-33 and 35-38 are drawn to a composition comprised of an antipsychotic agent, such as the elected compound, olanzapine, and an antagonist of the H_3 histamine receptor, such as the elected compound, 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether. The elected compounds are shown below:

Olanzapine:



3-(4-chlorophenyl)propyl-3-piperidinopropyl ether:

Todd teaches that intake of antipsychotic compounds such as olanzapine are associated with negative side effects, such as weight gain (p. 1, lines 8-11, and 26-37; p. 4, lines 4-10). Todd teaches that, to reduce weight gain, antipsychotic compounds such as olanzapine are administered with H_2 antagonists (p. 2, lines 5-20; p. 19, lines 17-19; p. 22, lines 12-24). Todd also teaches that the compounds can be administered separately, and also as a single composition (p. 22, lines 33-34; p. 23, lines 14-20). It is taught that combinations comprised of the antipsychotic agent olanzapine are preferred (p. 9, lines 4-6), and that the daily dosage of olanzapine ranges from 0.25 to 100 mg. (p. 19, lines 17-19). The preferred weight ratios of olanzapine/H_2 antagonist are taught as ranging from 1:150 (.0067) to 25:250 (.10) (p. 22, lines 12-19). The composition can be formulated as tablets, capsules, solutions, and other preparations (p. 24, lines 6-10).

Todd does not teach co-administration of olanzapine with histamine H_3 receptor inverse agonists or antagonists, such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether.

Schwartz et. al. teaches antagonist and agonist compounds of the histamine H_3 receptor such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether (Abstract; column 11, line 60; column 85-86, Table, No. 117). Schwartz et. al. teaches that 3-(4-

chlorophenyl)propyl-3-piperidinopropyl ether is effective in treating cognitive deficits associated with psychiatric pathologies, as well as obesity, attention deficits, and other disorders (column 1, lines 8-17; column 47, lines 34-38). It is also taught that the compound can be used in conjunction with psychiatric agents to improve their efficacy and reduce the side effects associated with the psychiatric drugs (column 50, lines 61-63). Oral administration is also taught (column 52, lines 6-12), as well as dosages from 10 to 500 mg. daily (column 52, lines 31-36).

Schwartz et. al. does not explicitly teach that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is present in a composition with olanzapine, or the specific dosage ratios of -(4-chlorophenyl)propyl-3-piperidinopropyl ether to olanzapine.

Schwartz et. al. teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is effective in treating side effects associated with psychiatric disorders and treatment, such as obesity, cognitive deficits, attention deficits, and other illnesses. Schwartz et. al. also teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether can be used in combination with psychiatric agents to reduce side effects associated with their intake. Todd teaches that when antipsychotic agents such as olanzapine are used in combination with H_2 histamine antagonists, weight gain, which is normally associated with olanzapine intake, is reduced. It would have been obvious for one of ordinary skill in the art to formulate a composition comprised of olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, because Schwartz et. al. teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is effective in reducing weight gain and treating cognitive and attention deficits associated with psychiatric pathologies, and can

be used with other psychiatric drugs, while Todd teaches that compositions comprised of olanzapine and H_2 histamine antagonists are effective in reducing weight gain associated with the drug. While Todd teaches a combination of olanzapine with H_2 antagonists rather than H_3 antagonists, such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, one of ordinary skill in the art would have been motivated to substitute the H_2 antagonists of the composition with histamine H_3 inverse agonists and antagonists, such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, because it is taught that the histamine H_2 antagonists and histamine H_3 inverse agonists and antagonists are effective in lessening weight gain associated with psychiatric drugs. Therefore, an expectation of success would have been expected by substituting the H_3 antagonist, 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, over histamine H_2 antagonists in the composition with olanzapine because both types of drugs have the same utility of reducing weight gain associated with psychiatric drug intake.

While Todd does not teach the weight ratio combination of olanzapine: 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether from 0.5 to 50 mg.:5 to 100 mg., or 3-20 mg. of olanzapine to 5 to 80 mg. of 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, it is taught that the ratio of olanzapine:histamine H_2 antagonist ranges from 1:150 (.0067) to 25:250 (.10). The weight ratio of olanzapine: 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether as instantly claimed ranges are from 0.5 mg.:100 mg. (0.005) to 50 mg.:100 mg. (0.5), or 3 mg:80 mg. (0.375), which is within the weight ratio ranges of olanzapine:histamine H_2 antagonist taught by Todd.

Claim Rejection-Obviousness Type Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 27-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-28 of copending Application No. 11/815736. Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass the same invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Instant claims 27-33 are drawn to a composition comprised of an antipsychotic or antidepressant, as well as an additional compound which is an antagonist or inverse agonist of the histamine H_3 receptor. The instant claims further include antidepressants such as mirtazapine, paroxetine, and antagonists of the histamine H_3 receptor such as

the compound 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, or a pharmaceutically acceptable salt of.

Claim 25 of the copending application is a dependent claim of claim 24, which is a dependent claim of claim 1. Claim 1 cites the HCl salt of the compound 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether. Claim 24 cites a composition comprised of the compound salt. Claims 25-28 are drawn to a composition comprised of 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether (hydrochloride salt), and additional antipsychotic and antidepressant agents such as mirtazapine, paroxetine, olazapine, and others. While the claims of the instant application explicitly exclude the chlorohydrate salts of 3-(4-chlorophenyl)propyl-3-piperidinopropylether, the preparation and therapeutic use of pharmaceutically acceptable salts, such as chlorohydrate salts, are well known in the art. Therefore, it would have been obvious to prepare and include pharmaceutically acceptable salts of 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether in the instantly claimed composition, and both sets of claims are not patentably distinct from each other.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627